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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/776,533	Applicant(s) ROGERS
	Examiner GIMBEL	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 7/11/02

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 2/7/01 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Applicant's amendment, filed 7/12/02 (Paper No. 4), has been entered.
Claims 13-17 have been canceled.

Claims 1-12 are pending.

2. To avoid possible confusion in matching papers, applicant is invited to review the spelling of the names on the line for Applicant in communications to the PTO.
For example, "Rodgers" should be "Rogers" and "Elazar" should be "Elazer".

3. Applicant's election with traverse of Group I (claims 1-12) on methods of inhibiting restenosis or stenosis with anti-Mac-1 antibodies in Paper No. 4 is acknowledged. The traversal is on the ground(s) that this is not the same restriction as set forth in the parent application USSN 08/823,999; that the claims are linked by a common function (modulation of vascular healing by inhibition of leukocyte function; and that the restriction requirement is based upon the insertion of limitations into the claims not present.

This is not found persuasive because of the reasons of record set forth in Paper No. 7.

It was noted that prior to setting forth the restriction requirement, it was pointed out that the claims are drawn to patentably distinct methods relying upon patentably distinct products as they read on adhesion molecule receptors and ligands. As disclosed on pages 7-8 of the instant specification (Composition), the methods rely upon compositions as they read on antibodies, ligands, proteins, antisense oligonucleotides, ribozymes and peptidomimetics are directed to patentably distinct adhesion molecules, wherein the compounds as well as the adhesion molecules differ in structure and modes of action to such an extent and require non-coextensive searches to such an extent that they are considered separately patentable. Therefore, the restriction was set forth for each of the various groups, irrespective of the format of the claims, because these are not proper species.

For convenience, the Groups were set forth as they read on adhesion molecules or adhesion molecule-specific antibodies only in the Restriction sent in Paper No. 3.
Further, it was noted the instant specification discloses a number of patentably distinct agents (e.g. pages 7-8, Composition), which may be subject to further restriction and/or species election. (e.g, antisense oligonucleotides and ribozymes as they read on a adhesion molecule receptor or ligand)
The Groups that were set forth appeared to read on the claims as currently recited, but would be subject to further Restriction and/or species election depending on the claimed recitation.

Applicant was invited to clearly elect a single Group as it reads on a particular therapeutic agent and to provide an appropriate claim that reads on the elected invention.

Consistent with the restriction of record, the examiner notes that the "compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" employed in the claimed methods (and the subject of the patentably distinct Groups) do not share a substantial structural feature essential to a common utility. In addition, a person of ordinary skill in the art would not envision one in view of the other. Again, the methods rely upon compositions as they read on antibodies, ligands, proteins, antisense oligonucleotides, ribozymes and peptidomimetics are directed to patentably distinct adhesion molecules, wherein the compounds as well as the adhesion molecules differ in structure and modes of action to such an extent and require non-coextensive searches to such an extent that they are considered separately patentable.

Applicant has not identified a common structural feature(s) essential to the common utility of "compounds (e.g. antibodies to different integrins; antibodies versus soluble receptors versus antisense oligonucleotides; etc., etc., etc.) which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue"

Applicant has not identified or provided evidenced that the asserted species or "compounds" are obvious variants nor has admitted this on the record.

Even though inventions were grouped together in a requirement in a parent application, restriction or election among the invention may be required in the divisional application, if proper. See MPEP 811.04.
It is noted that this is a continuation and not a divisional of parent application USSN 08/823,999.

In order to advance compact prosecution, the restriction set forth in Paper No. 3 relied upon reading the claims in light of the specification to determine the "compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" .
It appears that instant claim 10, drawn to the use of anti-Mac-1 antibodies, provides the only pending claim that provides sufficient specificity that particularly points out and distinctly claims the subject matter which applicant regards as the invention.

Claims 1-12 which read on methods of reducing or inhibiting stenosis or restenosis with anti-Mac-1 antibodies are under consideration as being drawn to the elected invention.

Applicant's arguments are not found persuasive.

The requirement is still deemed proper and is therefore made FINAL.

4. Applicant's request for petition is noted but will not be considered, as it is untimely. At the time Paper No. 4 was filed, the Restriction Requirement had not been made FINAL.

5. Applicant's provision of an Information Disclosure Statement is acknowledged. No references were provided by applicant in this application. The references have been considered given the availability of parent application USSN 08/823,999 at this time. However, the examiner has only made copies of those references cited in the instant Office Action for the instant file application. Applicant is invited to provide the references that are cited on the IDS but not cited in the instant Office Action to complete the instant file application. The examiner apologizes for any inconvenience to applicant in this matter.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, including the specificity of claimed/elected compounds.

7. Applicant is invited to review to the length of the Abstract to determine if it exceeds 150 words in length. See MPEP 608.01(b).

8. Formal drawings, filed 2/7/01, are acceptable.

9. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is required to identify the nucleotide and amino acid sequences in the specification with SEQ. ID NOS. See page 13, paragraph 3 of the instant specification. Applicant is invited to review the specification for compliance. See 37 CFR 1.821(d).

Appropriate corrections are required.

10. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. It is acknowledged that the claims are read in light of the elected invention as it reads on methods of inhibiting restenosis or stenosis with anti-Mac-1 antibodies.

In the interest of compact prosecution, the following rejections under 35 U.S.C. § 112, first paragraph, written description and enablement, are drawn to the recitation and scope of "compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" currently recited in the instant claims.

Applicant should provide independent claims drawn to the elected invention.

12. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 1-9 and 11-12 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing any "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" currently recited in the instant claims because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the claimed "compounds" including "antibodies, ligands, proteins, antisense oligonucleotides, ribozymes and peptidomimetics" which encompass patentably distinct adhesion molecules (and pathways) and inhibitory compounds, wherein the compounds as well as the adhesion molecules differ in structure and modes of action (see Composition on pages 9-20 of the instant specification).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species of "compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function" such as anti-Mac-1 antibodies to support an entire genus of diverse and unrelated molecules and adhesion pathways. The instant invention encompasses any "compound" or antagonist that results in the desired binding and inhibitory effect, yet the instant specification does not provide sufficient written description as to the structural features of said "compounds" and the correlation between the chemical structure and the desired binding and inhibitory function.

The reliance on the disclosed limited number of known adhesion molecules or adhesion molecule-specific antibodies does not support the written description of any "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated binding antagonists encompassed by the claimed "compounds" other than certain adhesion molecules or adhesion molecule-specific antibodies would be expected to have greater differences in their activities. "Compounds" encompassing "antibodies, ligands, proteins, antisense oligonucleotides, ribozymes and peptidomimetics" rely upon a myriad of distinct and diverse structures and do not encompass common structural elements essential to the common utility of "specifically inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue".

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

Hemker et al. (Emerging Drugs 4: 175-195, 1999) disclose that the hemostatic-thrombotic system is a non-linear system containing a number of nested positive and negative feedback loops and that at the present state of knowledge it is impossible to predict the effect of inhibition of a single reaction on the response of the complete system. For this reason, one cannot predict the antithrombotic potency of a compound from its biochemical properties. See entire document, including Summary on page 175.

For example, the instant specification relies upon screening for peptide and peptidomimetics compounds (pages 11-13) as well as screening for antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds (pages 13-19). The specification appears to disclose only one peptide, that is, a particular fibrinogen fragment which modifies fibrinogen to Mac-1 described by Altieri et al. J. Biol. Chem. 268: 1847-1853 (1993) (see page 12, paragraph 3 of the specification).

With respect to the breadth of "compounds", there is no written description of the wide variety of distinct and diverse compounds (e.g. for antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds). For example, applicant relies upon theoretical calculations and empirical findings for providing guidance for the design of oligonucleotides to inhibit gene expression and yet no written description of such inhibitory oligonucleotides compounds are disclosed in the specification as filed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Therefore, the elected invention of anti-Mac-1 antibodies (as well as certain soluble adhesion molecules and adhesion molecule-specific antibodies as well as the fibrinogen peptide discussed above disclosed in the specification as filed), but not the full breadth of the claimed "compounds", meets the written description provision of 35 USC 112, first paragraph.

Applicant has not provided sufficient written description of a "compound which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" broadly encompassed by the claimed invention.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. Claims 1-9 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as pharmacological compounds which inhibit stenosis or restenosis can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo evidence of inhibiting leukocyte-integrin-mediated adhesion with Mac-1-specific antibodies accurately reflects the relative efficacy of the claimed methods relying upon any "compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion or function" (e.g. compounds, molecules, peptides, peptidomimetics, anti-sense oligonucleotides, etc.).

Although the claims are read in the context of the anti-Mac-1 antibodies as the elected compound of the claimed invention; the following is noted as the claims read on "a compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion".

The instant claims encompass and are broadly drawn to "compounds" which encompass any compound, integrin, ligand, molecule, peptide or peptidomimetics or others disclosed on pages 9-20 of the instant specification is capable of inhibiting or reducing leukocyte-integrin-mediated adhesion to inhibit or reduce stenosis or restenosis. However, the claims do not recite sufficient structural elements or specificity for the "compounds" encompassed by the claimed methods. The specification does not provide sufficient guidance and direction to identify and to enable any "compound" which might inhibit or reduce leukocyte-integrin-mediated adhesion which inhibits or reduces stenosis or restenosis.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4) (1449).

The success of state of the art structure-based strategies for inhibitor design is highly unpredictable. For example, Kuntz, Science (1992) 257:1078-1081 on page 1080, column 3, discloses that as little as 2% of compounds predicted to inhibit specific enzymatic or receptor systems actually show inhibition in the micromolar range. Kuntz further discloses that "optimization" of these compounds has proven even more problematic.

Hemker et al. (Emerging Drugs 4: 175-195, 1999) disclose that the hemostatic-thrombotic system is a non-linear system containing a number of nested positive and negative feedback loops and that at the present state of knowledge it is impossible to predict the effect of inhibition of a single reaction on the response of the complete system. For this reason, one cannot predict the antithrombotic potency of a compound from its biochemical properties. See entire document, including Summary on page 175.

Topol et al. (JAMA 278: 479-484, 1997) states that a large number of pharmacological agents have failed to reduce restenosis or improve long-term clinical outcomes and that only the large-scale trial that reported an effect was using abciximab (see page 479, right hand column).

It is noted that this study by the EPIC Investigator Group reads on the elected invention, which is considered enabled, and also is met by the prior art teachings set-forth herein. It is noted that the referenced abciximab is a monoclonal antibody fragment against αIIbβ3, which cross-reacts with Mac-1 and is derived from the 7E3 antibody of certain prior art rejections. Also, the prior art does teach targeting Mac-1 with Mac-1-specific antibodies to inhibit ischemia-reperfusion injury associated with angioplasty and, in turn, the inhibition of stenosis and restenosis. See below.

Page 2, paragraph 2 of the instant specification discloses that attempts to limit stenosis or restenosis of blood vessels following revascularization have included administration of pharmacologic agents and technical approaches and that no pharmacologic agents has yet been shown to reduce restenosis in humans.

Therefore, the specification is consistent with the art recognized difficulties and unpredictability of making and using "compounds" which can reduce and inhibit stenosis and restenosis.

Applicant is relying upon a limited number of working examples in experimental models (e.g. M1/80 antibody in Examples 1 and 2 in the specification as filed) which would not be predictive of the ability of a large genus of diverse pharmacological agents to reduce or inhibit stenosis or restenosis in vivo in a clinical setting, as encompassed by the claimed methods.

For example, the instant specification relies upon screening for peptide and peptidodmimetics compounds (pages 11-13) as well as screening for antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds (pages 13-19). The specification appears to disclose only one peptide, that is, a particular fibrinogen fragment which modifies fibrinogen to Mac-1 described by Altieri et al. J. Biol. Chem. 268: 1847-1853 (1993) (see page 12, paragraph 3 of the specification).

The claims are not limited to the use of a single class of compounds but rather encompass a broad range of distinct compounds and specificities. The claimed methods encompass targeting a variety of integrin members (e.g. CD11a/CD18; CD11b/CD18; CD11c/CD18; CD11d/CD18) (or their ligands) and administering a variety of structural diverse compounds (e.g. antibodies, molecules, peptides, peptidomimetics, antisense oligonucleotides, ribozymes).

There is insufficient objective evidence that a single compound such as the M1/70 antibody in experimental models, as disclosed in the specification as filed, can be extrapolated to predict the efficacy of a myriad of diverse "compounds that inhibit or reduce leukocyte mediated adhesion or function" (e.g. molecules, peptides, peptidomimetics, oligonucleotides) in the claimed methods to inhibit or reduce stenosis or restenosis, commensurate in scope with the claimed invention.

There is insufficient objective evidence that the skilled artisan would predict that such a diverse class of compounds specific for various targets would be recognized as a single class of compounds to reduce or inhibit stenosis or restenosis of a blood vessel following injury to vascular tissue.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species such as anti-Mac-1 antibodies to support an entire genus of diverse and structurally unrelated compounds targeting a diverse adhesion molecules ligand-receptor molecules, interactions and functions. The instant invention encompasses any "compound which specifically reduces or inhibits leukocyte integrin-mediated adhesion or function" that results in the desired reduction or inhibition of stenosis or restenosis", yet the instant specification does not provide sufficient guidance and direction as to the structural features of said "compounds" and the correlation between the chemical structure and the desired binding and inhibitory function. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated binding antagonists encompassed by the claimed binding "compounds" would be expected to have greater differences in their activities

The scope of the required enablement varies inversely with the degree of predictability involved and in cases involving unpredictable factors such as physiological activity more may be required. See MPEP 2164.03 and 2164.02.

Given the relatively incomplete understanding in the biotechnological field involved and the lack of a reasonable correlation between the narrow disclosure in the specification and broad scope of protection sought in the claims; the lack of enablement is deemed appropriate. See MPEP 2164.08.

In view of the lack of predictability of the art to which the invention pertains, methods of reducing or inhibiting stenosis or restenosis with a broad range of structurally diverse "compounds" to a variety of diverse specificities would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies for inhibiting restenosis and stenosis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive for the breadth of "compounds" which specifically inhibits or reduces leukocyte-integrin-mediated adhesion that reduce or inhibit stenosis and restenosis.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined *under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e))*.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995) (1449).

Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

17. Claims 1-12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Coller et al. (U.S. Patent No. 5,976,532), as further evidenced by Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995) (1449).

Coller et al. teach the use of the 7E3 antibody to treat a number of thrombotic conditions, including providing 7E3 prior to angioplasty in effective amounts sufficient for inhibition of platelet aggregation as well as to prevent or reduce reocclusion that can occur after thrombolysis (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7, Examples and Claims). Here, Coller et al. also teach that effective amounts can be given parenterally in pharmaceutical acceptable vehicles encompassed by the claimed limitations by administering the antibody before, alone with or subsequent to be administered with a thrombolytic agent or anticoagulant in amounts sufficient to prevent platelet aggregation that can result in reocclusion (Utility of Platelet-specific Chimeric Immunoglobulin). Coller et al. Also teach that the antibodies can be used in a variety of situations including prevent thrombosis in a pulmonary embolism, transient ischemic attacks, deep vein thrombosis, coronary bypass surgery, surgery to insert a prosthetic vessel as well as angioplasty procedures encompassed by the claimed methods (see columns 5-6, overlapping paragraph).

Simon et al. provides evidence that the 7E3 antibody cross-reacts with Mac-1 (see entire document).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies in a number of thrombotic conditions, resulting in the inhibition or reduction of stenosis and/or restenosis. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

18. Claims 1-12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Co et al. (U.S. Patent No. 6,210,671).

Co et al. teach methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1). Co et al. teach that the antibodies can be administered before during or after the administration of thrombolytic agents or angioplasty (column 18, paragraph 4). Co et al. teach administering the antibodies parenterally in pharmaceutical compositions along with suitable carriers encompassed by the claimed invention in effective amounts that would known or apparent to the skilled artisan (column 20, paragraph 1-4).

It is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods encompassed by the referenced combination therapy including the use of anti-CD11b antibodies in methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty resulting in the inhibition or reduction of stenosis and/or restenosis.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

19. Claims 1-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Todd et al. (U.S. Patent No. 4,935,234) (see entire document).

Todd et al. teach methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD11b- (i.e. Mac-1-) specific antibodies (see entire document, including Claims). Todd et al. teach providing the CD11b-specific antibodies prior to intervention as well as in single or multiple doses to attenuate the inflammatory responses (see column 1, paragraph 1). Todd et al. teach that myocardial ischemia results from occlusion, reperfusion in the presence of a critical stenosis or narrowing of a blood vessel (e.g. column 6, paragraph 4). One of ordinary skill in the art would have immediately envisage that providing the anti-CD11b antibody in therapeutic methods would have encompassed providing the antibody in a pharmaceutical composition comprising at least a "solution". One of ordinary skill in the art at the time the invention was made would have immediately envisaged that the referenced teaching the insertion of balloon catheters in the circulatory system would have referred to angioplasty.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods encompassed by the referenced combination therapy including the use of anti-CD11b antibodies in methods of therapeutic treatment of ischemia-reperfusion injuries resulting in the inhibition or reduction of stenosis and/or restenosis.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

20. Claims 1-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995) AND/OR Co et al. (U.S. Patent No. 6,210,671) AND/OR Todd et al. (U.S. Patent No. 4,840,793) AND/OR Coller et al. (U.S. Patent No. 5,976,532)

Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Simon et al. differs from the referenced methods by not disclosing providing the antibody prior to and after the intervention per se.

Providing the antibody prior to and after intervention was well known and practiced at the time the invention was made, as taught by Co et al., Todd et al. and/or Coller et al.

Co et al. teach methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1). Co et al. teach that the antibodies can be administered before during or after the administration of thrombolytic agents or angioplasty (column 18, paragraph 4). Co et al. teach administering the antibodies parenterally in pharmaceutical compositions along with suitable carriers encompassed by the claimed invention in effective amounts that would known or apparent to the skilled artisan. (column 20, paragraph 1-4)

It is noted that Co et al. differs from the claimed invention by not disclosing the terms stenosis and restenosis per se. However, given the referenced methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (columns 17-18, overlapping paragraph and column 18, paragraph 3-4), the ordinary artisan would have had an expectation of success that anti-CD11b antibodies would have inhibited or reduced restenosis or stenosis.

Co et al. also differs from the not disclosing the use of anti-CD11b antibodies in the absence of L-selectin-specific antibodies per se.

Todd et al. teach methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD11b- (i.e. Mac-1-) specific antibodies (see entire document, including Claims). Todd et al. teach providing the CD11b-specific antibodies prior to intervention as well as in single or multiple doses to attenuate the inflammatory responses (see column 1, paragraph 1). Todd et al. teach that myocardial ischemic results from occlusion, reperfusion in the presence of a critical stenosis or narrowing of a blood vessel (e.g. column 6, paragraph 4). One of ordinary skill in the art at the time the invention was made would have readily understood that the referenced teaching the insertion of balloon catheters in the circulatory system would refer to angioplasty.

Coller et al. teach the use of the 7E3 antibody to treat a number of thrombotic conditions, including providing 7E3 prior to angioplasty in effective amounts sufficient for inhibition of platelet aggregation as well as to prevent or reduce reocclusion that can occur after thrombolysis (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7, Examples and Claims). Here, Coller et al. also teach that effective amounts can be given parenterally in pharmaceutical acceptable vehicles encompassed by the claimed limitations by administering the antibody before, alone with or subsequent to be administered with a thrombolytic agent or anticoagulant in amounts sufficient to prevent platelet aggregation that can result in reocclusion (Utility of Platelet-specific Chimeric Immunoglobulin). Coller et al. also teach that the antibodies can be used in a variety of situations including prevent thrombosis in a pulmonary embolism, transient ischemic attacks, deep vein thrombosis, coronary bypass surgery, surgery to insert a prostethic vessel as well as angioplasty procedures encompassed by the claimed methods (see columns 5-6, overlapping paragraph).

Although certain references do not disclose the targeted endpoint of reducing or inhibiting stenosis or restenosis per se, it was clear that the references do teach inhibiting ischemic-reperfusion injuries or complications associated with thrombotic conditions, including angioplasty. Given the well known complications of stenosis and restenosis associated with angioplasty at the time the invention was made, one of ordinary skill in the art would have had an expectation of success that treating these conditions or procedures with effective amounts of anti-Mac-1 antibodies to inhibit platelet-mediated complications, including those associated with angioplasty would have resulted in the inhibition or reduction of stenosis or restenosis as well.

The different references differ from the claimed methods by not disclosing all of the known targeted conditions complicated by stenosis or restenosis as recited in claim 3.

Given the combined teachings which including teachings of administering antibodies that bind Mac-1 / CD11b to treat or to prophylactically treat a number of thrombotic conditions such as angioplasty and bypass surgery encompassed by the claimed methods, one of ordinary skill in the art would have been motivated to apply anti-Mac-1 antibodies to inhibit or reduce stenosis or restenosis in these various modalities with an expectation of success at the time the invention was made. It was well known by the ordinary artisan at the time the invention was made that angioplasty, atherectomy endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery or transplantation of cells, tissues or organs was complicated by stenosis or restenosis. Given the combined teachings of reducing or inhibiting thrombotic-related conditions in a number of modalities including those encompassed by claim 3 as well as the common occurrence of stenosis and restenosis in the vascular intervention, injuries and diseases as well as transplantation encompassed by claim 3, it would have been obvious to one of ordinary skill in the art to apply said anti-Mac-1 antibodies in the various conditions encompassed by claim 3.

Further, the composition forms set forth in claim 4 were well known and practiced at the time the invention wad made, as taught by Co et al. and Coller et al..

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 1-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending application Serial No. 08/823,999. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same or nearly the same methods of inhibiting stenosis or restenosis in the same or nearly the same methods of cardiovascular condition with the same anti-Mac-1 antibodies, as the elected invention.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILIP GAMBEL

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September 5, 2002